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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,576	04/28/2006	Weon Kyoo You	P10014US	2928

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THE RAFFERTY PATENT LAW FIRM
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EXAMINER	
MOORE, WILLIAM W	
ART UNIT	PAPER NUMBER
1656	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,576	YOU ET AL.	
	Examiner	Art Unit	
	WILLIAM W. MOORE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 April 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20080423*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

Applicant's claim in the Declaration of Inventorship filed 28 April 2006 to priority of the 31 October 2003 filing date of the International patent application PCT/KR2003/002316, of which the instant application is a national stage filing under 35 U.S.C. § 371, is hereby acknowledged. Applicant is invited to amend the first page of the specification to provide the continuing data for the instant application by setting forth the cited International application in the chain of priority.

Information Disclosure Statement

Applicant's Information Disclosure Statement [IDS] filed 23 April 2008 is hereby acknowledged.

Objection to the Specification

This application contains a sequence disclosure that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason: A decapeptide sequence subject to the definition of 37 CFR 1.821(a)(2) is set forth at line 15 of page 15 but is not separately identified by a sequence identification number. Applicant's attention is directed to 37 CFR 1.821, which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Thus, the reference to the decapeptide at page 15 must either be (i) replaced at page 15 by the description "the sequence of amino acids from position 1 to position 10 of SEQ ID NO:1", or (ii) the provision of an amended Sequence Listing that includes the decapeptide with its particular SEQ ID NO as well as the statement of that new, particular, SEQ ID NO immediately after the decapeptide at page 15. Either format will bring the Specification into compliance with the requirements of 37 CFR 1.821 through 1.825.

Drawing Objection

The drawings are objected to because depictions of particular features in several Drawing Figures inadequately portray intended comparisons. In particular, the several depictions of rBAT activity in the legend box and vertical bars of Figure 1a, the dotted line depicting rBAT clotting velocity in Figure 1b, and the list of restriction endonuclease designations in Figure 2 are quite indistinct. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required

in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claims 1-6 are objected to because of the following informalities:

Claims 1 and 3 both lack a definite article at the beginning of each sentence.

The SEQ ID NO:1 to which claim 2 refers is the amino acid sequence of baxotrobin.

Claim 4 lacks the proper use of both definite and indefinite articles and is also objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim because it fails to make particular reference to the subject matter of claim 3 from which it depends. Amending claim 4 to state instead, "[A] method of preparing a thrombin-like enzyme comprising the culture and fermentation of the transformed *Pichia* GS115 cell of claim 3 and the isolation of the recombinant . . . therefrom", will overcome both aspects of this objection to the claim.

Claim 5 describes no medium and claim 4 describes no medium, thus claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim where its recitation "the medium" finds no antecedent basis in claim 4, and where its recitation of "the transformed microorganism" makes no particular reference to the subject matter of claim 3 from which it depends. Amending claim 5 to state instead, "The method according to claim 4 comprising incubating the transformed *Pichia* GS115 cell in a medium comprising . . . and a pH of . . . at a temperature of . . .", will overcome both aspects of this objection to the claim.

Claim 6 lacks the proper use of both definite and indefinite articles and twice recites the superfluous term "step to". Amending claim 6 to state instead "[A] method of preparing a . . .

comprising (a) obtaining an active fraction . . . and (b) purifying the recombinant . . . by applying the active fraction of step (a) . . . " will overcome this objection of claim 6.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected for lack of enablement because all require a specific biological material for the enablement of their various subject matters but the specification does not disclose that the claimed biological material, the vector pPIC-rBAT, is freely available to the public, either currently or upon the issuance of a patent having the claimed biological materials as subject matter. The present record provides no evidence of a deposit receipt of indicating that the fee for maintenance for 30 years of the deposit of a host cell that comprises the biological material designated pPIC-rBAT has been charged to and paid by the assignee. Applicant should note that deposits under the terms of the Budapest Treaty are, in themselves, insufficient to satisfy 37 CFR §§ 1.805-1.807 unless they are disclosed on the record to be freely available to the public should a U.S. patent issue on the instant application. See, *Ex parte Hildebrand*, 15 USPQ2d 1662, 1664 (1990) (restrictions must "be irrevocably removed upon the issuance of [a] patent" since Rule 9.2 of the Budapest Treaty contains a residual requirement of secrecy). See also, MPEP § 608.01(p)(C)(3). Applying 37 CFR § 1.801, et seq., to any deposit, including a Budapest Treaty deposits requires that an enabling disclosure based upon such a deposit be provided by submitting a declaration or averment, either by the assignee or the attorney of record over his or her signature and registration number, providing the following two assurances:

1) that all restrictions on the availability to the public of the deposited material will be removed, and,
2) that the viability of the deposits will be maintained,

both for the duration of the patent term or for a period of twenty years in accordance with 37 CFR §§ 1.805-1.807. See, MPEP §§ 2405-2411.05, wherein the latter section requires an amendment to the specification that introduces specific information concerning any deposit of biological materials. Such an amendment does not constitute new matter.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite in referring to both “preparation” and “process” but failing to clearly distinguish the latter from the former, thus cannot particularly point out any “process” that differs from a “preparation”. Amending claim 4 to generally follow the disclosures of Examples 3 and 4 at pages 14 and 15 of the specification, e.g., by reciting, "A method of preparing a thrombin-like enzyme comprising the culture . . . and the isolation of the . . . from the culture medium”, will overcome this aspect of the rejection.

Claim 5 is indefinite because it fails to particularly point out any particular medium in reciting ”the medium” where the mere recitations of a pH range, a temperature range, and a range of duration, of an incubation cannot convey any information about the nature of a medium wherein the transformed *Pichia* cells are maintained. Amending the claim to provide to indicate the nature of the medium, or media should they differ, in which transformed *Pichia* cells are maintained will overcome this aspect of the rejection.

Claim 4 is independently rejected, and claim 6 is rejected, for omitting essential method steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. There are two omitted steps in claim 4: (1) the expression of baxotrobin by the cells and (2) the recovery, or isolation, of the baxotrobin from the cell culture. The omitted step in claim 6 is the recovery of purified baxotrobin. Such recovery steps are required in order that the purposes expressed in the preambles of claims 4 and 6 be accomplished, and unless the purposes are accomplished, the claims are incomplete, thus indefinite. Similarly, unless claims claim 4 states an expression of the baxotrobin, the purpose stated in the claim preamble is not accomplished. Claim 5 is not included in this aspect of the rejection because it is clear that it is intended to describe, and may be amended to adequately describe as suggested in the preceding paragraph, the “culture and fermentation” portion of the method of claim 4.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 USC § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 are rejected under 35 USC § 103(a) as being unpatentable over **Maeda et al.**, JP 02-124092, in view of **An et al.**, CN 1370833 and **Chung et al.**, US 7,033,788, all made of record with Applicant's IDS.

Maeda et al. teach the recombinant expression of the mature baxotrobin, a serpent venom protease, the amino acid sequence of which is identical to that set forth in SEQ ID NO:1 herein, fused to an heterologous signal peptide in host cells of the yeast *Saccharomyces cerevisiae*. See the abstract, generally, and pages 6 and 28-29 of the publication itself for the teachings of, respectively, the yeast host and mature baxotrobin amino acid sequence. **An et al.** teach the insertion of a segment of a cDNA encoding a mature serpent venom protease, termed batroxibin, that shares significant amino acid sequence similarity to the amino acid sequence set forth in SEQ ID NO:1 herein in the expression plasmid pPIC9 at the multiple cloning site 3'-proximal to the nucleic acid sequence region encoding the α-factor peptide to provide a polynucleotide encoding a fusion of an α-factor peptide amino-proximal to a serpent venom protease and the subsequent transformation of host cells of the yeast *Pichia pastoris* GS115 with the expression vector to permit recombinant expression of the mature serpent venom protease by the transformed *Pichia* host cell. See the abstract, generally, and pages 4 and 11-14 of the publication itself for the teachings of, respectively, the mature serpent venom protease amino acid sequence and the insertion of its coding sequence in the pPIC9 vector and transformation of the *Pichia* GS115 host cell. **An et al.** further teach that which was already well-known in the art at the time the invention was made, that the serpent venom proteases represented both by their batroxibin and the baxotrobin of **Maeda et al.** are medically significant means for treating thrombolytic disease. See the abstract.

Chung et al. teach the use of an N–terminal primer comprising an oligonucleotide region encoding a protease KEX2 cleavage site adjacent to a region encoding an amino-proximal, mature, serpent venom polypeptide to generate a nucleotide sequence for insertion in the *Pichia* expression plasmid pPIC9 at the multiple cloning site 3'-proximal to the nucleic acid sequence region encoding the α-factor peptide to provide a polynucleotide encoding a fusion of an amino-proximal α-factor peptide, intervening KEX2 cleavage site, and carboxyl-proximal serpent venom polypeptide, as well as the transformation of a *P. pastoris* GS115 host cell with the vector and the incubation of the transformed cells in minimum glycerol medium at pH 6 and 30°C for a period of time adequate to achieve a desired cell density. See col. 8 at lines 5-46. **Chung et al.** then teach the harvesting of the transformed *Pichia* GS115 cells from the initial culture medium by centrifugation and their subsequent suspension in minimal methanol medium comprising 0.5% methanol for incubation at pH 6 and 30°C over a period of 96 hours during which methanol was replenished at 0.5% and induction of expression of the fusion polypeptide

encoded by the polynucleotide maintained by the pPIC9 vector permitted accumulation of the mature serpent venom polypeptide released after cleavage from the fusion polypeptide in the host cell, followed by recovery of the polypeptide from the culture medium. See col. 8, line 46, through col. 9, line 6.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare an expression vector indistinguishable on the present record from the pPIC-rBAT vector of claim 1 herein comprising the advanced pPIC9 expression vector amino-proximal α-factor peptide, intervening KEX2 cleavage site, and carboxyl-proximal serpent venom polypeptide design of **Chung et al.** wherein a nucleic acid sequence encoding the mature baxotrobin amino acid sequence of SEQ ID NO:1 herein, according to claim 2 herein, taught by Maeda replaces the similar serpent venom protease of **An et al.** This is because An et al. teach that which the skilled artisan would recognize, the medical significance of the class of serpent venom proteases and teach the use of the pPIC vector for the recombinant expression of the serpent venom protease, because **Maeda et al.** teach the amino acid sequence of such a medically significant serpent venom protease, and because **Chung et al.** teach the design of an expression construct based on the pPIC vector that permits the efficient recombinant production of a desired, mature, serpent venom polypeptide product, albeit not a protease, in *P. pastoris* host cells in predictable culture conditions. It would also have been obvious to one of ordinary skill in the art at the time the invention was made to transform a *P. pastoris* GS115 host cell according to claim 3 herein and to practice a method of preparing the mature baxotrobin having the amino acid sequence of SEQ ID NO:1 according to claims 4 and 5 herein. This is because both **An et al.** and **Chung et al.** teach the use of *P. pastoris* GS115 host cells for recombinant production and recovery of mature, medically significant, polypeptides as they in the venom of serpents and because **Chung et al.** teach the incubation media, temperatures, and other conditions for the efficient, recombinant, production of a mature serpent venom polypeptide by transformed *P. pastoris* GS115 host cells, where the period of the first incubation may vary according to the temperature used and terminal cell density desired, thus fall within the duration recited at line 3 of claim 5, that permit accumulation of the desired, mature, polypeptide in the culture medium from which it may be recovered, or isolated by a variety of methods well known in the art where claims 4 and 5 rejected herein require no particular method. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claim 6 is rejected under 35 U.S.C. § 103(a) as being unpatentable over **Maeda et al.**, **An et al.**, and **Chung et al.** as applied to claims 1-5 above, and further in view of **Itoh et al.**, made of record with Applicant's IDS, and **Boodhoo et al.**, US 6,881,404, made of record herewith

The teachings of **Maeda et al.**, **An et al.**, and **Chung et al.**, discussed above, are taken as before. Itoh et al. are now cited for their teaching of the purification of mature batroxobin, the amino acid sequence of which is identical to that set forth in SEQ ID NO:1 herein, "by chromatographies on Heparin Sepharose CL-6B, DEAE-Sephacel and Sephadex G-100". See lines 3 and 4 of the paragraph in the left column, page 3135, under the headings "Experimental Procedures" – "Amino Acid Sequence Determination". While Sephadex G-100 chromatography is a size-exclusion purification procedure and DEAE-Sephacel chromatography is an anion-exchange purification procedure, the Heparin Sepharose CL-6B chromatography taught by **Itoh et al.** is an affinity chromatography purification procedure as evidenced by the teachings at col. 3, lines 41-44, and col. 16, lines 10-13, of Boodhoo et al., of this affinity chromatography purification step for removing an active fraction of a serpent venom protease from an aqueous solution comprising the protease. Boodhoo et al. also teach that an active fraction of their serpent venom protease may be further purified by various other chromatographic procedures, including "hydrophobic interaction chromatography using", e.g., "phenyl ether" resins. It would have been obvious to one of ordinary skill in the art at the time to apply the teachings of **Itoh et al.** and **Boodhoo et al.** to the purification of the mature protease having the amino acid sequence set forth in SEQ ID NO:1 herein that accumulates in the culture medium of *P. pastoris* GS115 host cells upon recombinant expression by the cells obvious over teachings of **Maeda et al.**, **An et al.**, and **Chung et al.** by a method comprising an hydrophobic chromatography step and an affinity chromatography step because both **Itoh et al.** and **Boodhoo et al.** teach that affinity chromatography using a heparin-presenting resin is advantageously used in purifying a serpent venom protease and because Boodhoo et al. also teach that further, hydrophobic, chromatography is advantageously used in purifying a serpent venom protease. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr Bragdon, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/Nashaat T. Nashed/
Nashaat T. Nashed, Ph.D.
Supervisory Primary Examiner
Art Unit 1652

William W. Moore
24 April 2008